33. (New) A method for screening for atrophy of the antrum area of the stomach from blood, serum or plasma, such atrophy correlating with increased risk of gastric cancer, said method comprising:

a) determining the reference range of pepsinogen I and gastrin-17 for a population of normal individuals,

b) obtaining a blood, serum or plasma sample from a patient,

c) quantitatively measuring the pepsinogen-I concentration in said sample using an immunoassay and comparing the value obtained to a cut-off value for pepsinogen-I selected from a range that overlaps the reference range; and

d) quantitatively measuring the gastrin-17 concentration from said sample by immunoassay and comparing it to a cut-off value for gastrin-17 selected from a range that overlaps the reference range,

whereby if the pepsinogen-I concentration in said sample is increased compared to said cut-off value and the gastrin-17 concentration in said serum sample is decreased compared to said cut-off value then atrophy of the antrum area of the stomach is indicated.

REMARKS

Applicants have amended the claims to more clearly describe the invention. Support for the amendment "blood, serum or plasma" to claims 10, 11 and 31 can be found in the Specification on page 1, line 15. No new matter has been added. Instead, Applicants have

tried to streamline the language, setting forth the various steps of the method in a clear and concise manner.

Applicants wish to thank the Examiner for the courtesy she extended to Applicants' representative during the Interview of November 6, 2002. All of the claim rejections were discussed during the Interview. Applicants have amended the claims in accordance with the Examiner's suggestions as discussed. Applicants are especially appreciative for the Examiner's time and helpful comments offered to assist Applicants in moving this application towards allowance.

Response to Arguments

On page 2, section 2 of the Office Action, the Examiner indicates that she has reviewed the Declaration of Matti Harkonen, which was filed February 17, 2000. The Examiner indicates that this Declaration is insufficient to overcome the rejection of claims under 35 U.S.C § 103 over Varis, in view of Mulholland and Sipponen as set forth in the previous Office Action because the clarification and discussion provided by the Declaration is not commensurate in scope with the instantly claimed invention.

Applicants note that the Examiner confirmed that she had received the Declaration of Dr. Pentti Sipponen, which was dated November 2, 2000 and was submitted with the preliminary amendment filed in this application on March 14, 2001. Since this Declaration had been misfiled and therefore had not been considered, Applicants would appreciate the Examiner's confirmation that the Declaration has now been properly entered into the record and fully considered.

Claim Objections

The Examiner notes several informalities with claims. For example, a comma after the word "cancer" is missing from claim 2, line 2. Also, a "_" appears in claim 2, line 5 and claim 19, line 8. Lastly, claim 2, line 8, and claim 7, line 4 each contain a phrase that is enclosed by brackets. The Examiner indicates that the meaning of these informalities is unclear.

Applicants have amended the claims, correcting the noted informalities and thereby obviating the objections.

Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1-27 for recitation of the phrase "a serum sample" without indicating the source of the serum sample being analyzed. Applicants have overcome this rejection by amending the claim to indicate that the sample is from a patient, as suggested by the Examiner.

The Examiner has rejected claims 10-18 for failing to recite any specific cut-off or reference values for pepsinogen-1 and gastrin-17, contending that this makes the invention indistinctly claimed. Applicants offer the following for clarification.

The reference range refers to the range of values obtained from healthy individuals in a given population for a particular marker, such as pepsinogen-I or gastrin-17. Because of the variation within a population, however, the end-points of the range fall within a "gray" area. That is, in some cases where two individuals have an identical test value, one may display health and one disease, presumably based on genetic or lifestyle differences. Consequently, once the reference range is identified, cut-off values are selected. This

range of cut-off values overlaps the "gray" area of the endpoints of the test values found in individuals with disease as well as the test values found in normal individuals. These cut-off values can be increased or decreased depending on whether a false-positive or a false-negative is of more concern. Consequently, cut-off values typically cover the range of normal/disease overlap and allow researchers to better tailor a particular test to favor a particular ratio of false-positive/false-negative results. Applicants have amended claims 10-18 to more clearly describe these steps and to indicate how the critical values are obtained. Applicants thus request reconsideration and removal of the rejection.

The Examiner has rejected claims 1, 10 and 19 for recitation of the phrase "wherein said method comprises." The Examiner indicates that no active voice method claims are recited prior to the recitation of the "wherein" clause and suggests amending the claim to delete the word "wherein." Applicants have so amended the claims, thereby obviating the rejection.

The Examiner has rejected claims 1, 10 and 19 as being incomplete for omitting essential steps that amount to gap between the steps. The Examiner indicates that the omitted steps are: providing a sample from a patient and specific method steps for screening atrophy correlated with gastric cancer. Applicants have cancelled claim 19 and amended claims 1 and 10 to recite active voice method steps and to include providing a sample from a patient. Applicants therefore respectfully request reconsideration and removal of the rejection.

The Examiner rejects claims 3, 12 and 21 for recitation of the phrase "wherein the serum gastrin-17 concentration is also measured using the protein stimulation test." The Examiner indicates that this rejection could be obviated by amending the claim to recite

"further comprising" or a phrase that clearly conveys what is intended. Applicants have so amended the claims, thereby obviating the rejection.

The Examiner has rejected claims 1, 2, 4, 10-12, 20 and 22 as being incomplete for omitting essential elements that amount to a gap between the elements. The Examiner indicates that the omitted elements are: essential reagents for carrying out specified assays that need fluorescent and luminescent reagents and a reference standard for comparison. The Examiner indicates that reference to an assay that uses the recited indicators would obviate this rejection. Applicants have amended the claims to refer to an assay that uses particular indicators, thereby obviating the rejection.

The Examiner has rejected claims 9, 18 and 27 for recitation of the phrase "wherein the method is performed in combination with..." The Examiner indicates that no active voice method steps are recited and that the rejection could be obviated by amending the claims to recite "further comprising the step of..." Applicants have so amended the claims, thereby obviating the rejection.

The Examiner has rejected claim 19 as being indefinite for recitation of the phrase "a method for screening for atrophy of the corpus **and** antrum area of the stomach." The Examiner points out that the method states that corpus atrophy is defined by a pepsinogen-1 value below 30 µg/l and antrum atrophy is defined by pepsinogen-1 above 30 µg/l. The Examiner points out that a single sample cannot have both sets of values true at the same time. Applicants have amended the claim to delete the reference to antrum atrophy and have introduced this method in a new independent claim. Thus, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner has rejected claim 20 as being duplicative of claim 2. Applicants have amended the claim, thereby overcoming the rejection.

The Examiner has also rejected claim 20 for referring to a single "reference value" at line 6 and line 8 referring to a plurality of reference values. Applicants have amended the claims to recite an agreement in tense.

Rejection Under 35 U.S.C. § 102

The Examiner has rejected claim 10, 11 and 13-15 as being anticipated by Chen et al. (1994). The Examiner contends that Chen et al. disclose "a method of screening for atrophy in the antrum area (duodenal ulcer, see page 1514, col. 1, paragraph 1) of the stomach..." By determining pepsinogen-1 and gastrin-17 levels in a serum sample, and comparing the levels with a cut-off and reference value for pepsinogen-1 and gastrin 17 levels. The Examiner contends that this reference anticipates the claimed invention in light of these claims not reciting any specific cut-off or reference values. Applicants respectfully traverse.

The reference range refers to the range of values obtained from healthy individuals in a given population for a particular marker, such as pepsinogen-I or gastrin-17. Because of the variation within a population, however, the end-points of the range fall within a "gray" area. That is, in some cases where two individuals have an identical test value, one may display health and one disease, presumably based on genetic or lifestyle differences. Consequently, once the reference range is identified, cut-off values are selected. This range of cut-off values frequently overlaps the "gray" area of the endpoints of the test values found in individuals with disease as well as the

test values found in normal individuals. These cut-off values can be increased or decreased depending on whether a false-positive or a false-negative is of more concern. Consequently, cut-off values typically cover the range of normal/disease overlap and allow researchers to better tailor a particular test to favor a particular ratio of false-positive/false-negative results. For example, it may be more desirable to give a drug associated with severe side effects to only those individuals certain to have the disease. Here, the cut-off value would be selected so that individuals representing false positives were excluded. On the other hand, including individuals representing false positives might be preferable for a non-invasive test that, for example, monitors heart disease.

Once the reference range and cut-off value range have been identified, a blood, serum or plasma sample is taken from a patient. This serum sample then undergoes an immunological assay that provides a value for the concentration of pepsinogen-1 and/or gastrin-17. The patient sample values are then compared to the reference range and the cut-off values that have been selected. The location of atrophy in the stomach is predicted as follows:

Antrum	Pepsinogen-1 higher than cut-off value
	Gastrin-17 lower than cut-off value
Whole Stomach	Pepsinogen-1 higher than cut-off value
	Gastrin-17 within the reference range
Corpus	Pepsinogen-1 lower than cut-off value

	Gastrin-17 higher than reference range

Exhibit 1 is a schematic of the stomach and the duodenum that indicates the delineation of the various areas in these structures.

Applicants first note that the duodenum is defined as "the first part of the intestine immediately beyond the stomach, so named because its length is about 12 finger breaths." (Blacks Medical Dictionary, 39th Edition, 1999, MacPherson *Eds.*, Madison Books, New York). The Chen reference is directed to a study of patients that have duodenal ulcer disease. As can be seen by the definition of duodenum, this structure is different from the stomach. That is, while the duodenum is adjacent to the stomach, it is a separate and distinct anatomical part that is physically separate from the stomach and that has a different physiological function. Since a reference supporting a novelty rejection must contain each and every element of the claimed invention, the Chen reference cannot be used because it does not speak to any portion of the stomach, but only to the duodenum.

The Chen reference teaches increased pepsinogen-1 and serum gastrin concentration in patients with duodenal ulcer disease (page 1511, column 1, first three lines of text). The authors of this reference found that eradication of *H. pylori* caused a fall in serum pepsinogen-1 and gastrin-17 levels.

First, Applicants point out that the instant invention is not dependent on the presence of *H. pylori* bacteria or infection. Second, the instant invention makes no statement regarding the comparison of pepsinogen-1 and gastrin-17 levels after eradication of any *H. pylori*, as taught by Chen (page 1512, lines 37-38 and column 2, lines 18-19). Lastly, Chen teaches a decrease in both pepsinogen-1 and gastrin-17 levels. As indicated in the chart

above, the instant invention does not describe a situation in which both the pepsinogen-1 and gastrin-17 levels decrease. In atrophy of the antrum, the pepsinogen-1 levels increase while the gastrin-17 levels fall. In atrophy of the whole stomach, the pepsinogen-1 falls, but the gastrin-17 levels remain within the reference range. In atrophy of the corpus, while pepsinogen-1 levels fall, gastrin-17 levels increase. Thus, Chen fails to teach any one of the three combinations that are present within the claims of the instant invention. As a consequence, Chen cannot serve as an anticipatory reference.

In view of the above, Applicants respectfully request reconsideration and removal of the rejections.

Rejection Under 35 U.S.C. § 103

The Examiner has rejected claims 1-3, 6-7, 9 and 10 as being unpatentable over Wu et al. (1994) in view of Mulholland et al. (1993). The Examiner contends that Wu et al. teach a method of screening for atrophy that correlates with increased risk of gastric cancer in patients with gastric ulcer, duodenal ulcer or ulcer of the whole stomach. This method comprises the steps of determining the serum levels of *H. pylori* antibodies, pepsinogen-1 and gastrin, but fails to teach measurements of gastrin-17 or a reference range for gastrin-17.

The Examiner contends that Mulholland et al. teach an immunoassay for determining gastrin-17 levels that correlates with the presence of *H. pylori* infection. Here, the gastrin-17 value of *H. pylori* infected patients was increased over the reference level. The Examiner contends that it would have been obvious to a skilled artisan to measure

gastrin-17 as taught by Mulholland because Mulholland teaches that blood levels of gastrin-17 are associated with *H. pylori* infection. Applicants respectfully traverse.

The instant invention is a method for screening for atrophy in the stomach, which uses measurements of pepsinogen-1 and gastrin-17. Here, the reference range for pepsinogen-1 and gastrin-17 are first determined in a given population. For example, a normal population of Finnish men over the age of 50 may have a reference range for pepsinogen-1 of 25-120 µg/l and a reference range for gastrin-17 of 2-25 pmol/l. The upper and lower limit of the reference range can and will vary according to the particular population. For example, the reference ranges for pepsinogen-1 for Chinese men over age 50 who smoke may be very different from that of a nonsmoking Finnish population. In addition, the reference ranges may vary according to gender, age and ethnicity. While these variations may be slight, it may be possible to reduce the number of false-negatives and false-positives by identifying the reference range for the specific population of which the patient is a member.

The Wu abstract indicates that the authors used for their analysis the value of pepsinogen-1 alone, the pepsinogen-1 value multiplied by the gastrin value, or the pepsinogen-1 value divided by the gastrin value. This is significantly different from the instant invention where it is a particular combination of pepsinogen-1 and gastrin-17 values as compared to cut-off values and a reference range.

The Mulholland reference looks at the pepsinogen-1 and gastrin-17 serum levels in patients with a history of duodenal ulceration. As discussed above for the Chen reference, the duodenum is a separate anatomical and physiological structure from the stomach. In addition, it is known in the art that duodenal ulcer decreases the risk for gastric cancer.

These two facts alone would discourage the skilled practitioner from combining the Mulholland et al. reference with that of Wu since Mulholland would teach away from an increased risk of gastric cancer.

The Mulholland reference also indicates that *H. pylori* bacteria or infection raises circulating gastrin concentrations (page 757, first four lines of text, column 1). It also indicates that eradication of *H. pylori* lowers the gastrin concentration (page 757, column 2, lines 2-5). The teaching that *H. pylori* infection increases gastrin-17, which falls after eradication of the infection, is similar to the teaching of Chen and is a result of the fact that *H. pylori* infection causes an inflammation that leads to an increased permeability of the G-cells, thereby raising the gastrin-17 serum concentration. According to Mulholland, this increase may be one reason for predisposition to duodenal ulcer. This, however, is not related to and does not mean a predisposition for gastric ulcer, which is the risk factor for gastric cancer acknowledged by Wu.

These two references cannot be properly combined simply because both references mention *H. pylori*. The instant invention as discussed above, does not require the presence of *H. pylori* bacteria or require an *H. pylori* infection. In fact, in very advanced atrophy, which has the highest cancer risk, *H. pylori* bacteria cannot survive. Thus, in view of the above, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner has rejected claims 1-3, 6-7 and 10 as being unpatentable over Varis (1991) in view of Mulholland et al. (1993) and Sipponen et al. The Examiner contends that Varis teaches a method of screening for atrophy that correlates with increased risk of gastric cancer in patients which comprises the step of determining the serum levels of pepsinogen-1 and gastrin and comparing these to cut-off levels and a reference range.

The Examiner acknowledges that the reference does not teach the measurement of gastrin-17 or a reference limit for gastrin-17.

The Examiner contends that Sipponen et al. teach *H. pylori* infection that is associated with atrophy of the antrum and corpus of the stomach in an analogous art.

The Examiner contends that Mulholland et al. teach an immunoassay for determining serum gastrin-17 levels that correlates with the presence of *H. pylori* infection. The Examiner contends that it would have been obvious to one of ordinary skill in the art to combine the method of Varis with that of Mulholland because Mulholland teaches that gastrin-17 levels are associated with *H. pylori* and Sipponen and Mulholland teach *H. pylori* to be a co-factor for increased risk of cancer. Applicants respectfully traverse.

As discussed above, Mulholland does not teach that *H. pylori* infection (or associated gastrin-17) is a cofactor of gastric cancer. Mulholland teaches only that *H. pylori* causes duodenal ulcer, which is not a precondition of atrophy of the stomach or gastric cancer. Mulholland also teaches that *H. pylori* is associated with an increased level of gastrin-17. Duodenal ulcer does not present a risk of gastric cancer, whereas atrophy of the corpus or antrum does. Advanced atrophy of the corpus reduces the secretion of hydrochloric acid in the stomach, which is a poor environment for the *H. pylori* bacteria. Thus, this decreases the risk for ulcer ("no acid, no ulcer") although the cancer risk is increased.

Sipponen does not discuss pepsinogen nor gastrin at all in connection with gastric cancer, only the various forms of cancerous conditions and corresponding status of the gastric mucosa and possible existence of *H. pylori*. Applicants respectfully submit that the

Examiner is using hindsight to introduce the *H. pylori* infection and duodenal ulcer into the discussion in order to make the bridge from total gastrin to specific gastrin-17.

Applicants submit that the references are not combinable because Varis does not discuss *H. pylori* nor duodenal ulcer, but atrophic conditions. Atrophic conditions are often *H. pylori* free. Mulholland discusses duodenal ulcer, which is not associated with atrophic conditions of the stomach. There is no incentive for the skilled artisan to improve the teachings of Varis by turning to a document that teaches the use of a different disease condition. In addition, Mulholland teaches against Varis in the sense that Mulholland focuses on increased marker values for gastrin-17 in duodenal ulcer disease, whereas Varis teaches reduced values of serum gastrin. Thus, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner has rejected claims 1, 2, 4-7, 9-16, 18, 20-25 and 27 as being unpatentable over Plebani (1993) in view of Mulholland et al. The Examiner contends that Plebani teaches a method of screening for atrophy that correlates with increased risk of gastric cancer by determining the serum levels of pepsinogen-1, gastrin and *H. pylori*. These levels are then compared to cut-off levels of pepsinogen-1, but fails to teach the measurement of gastrin-17, reference ranges for gastrin-17, gastrin-17 levels before and after a meal and the use of antibodies to detect gastrin-17.

Plebani measures pepsinogen-1 and total gastrin and suggests using the pepsinogen-1 value and an index of pepsinogen-1 multiplied by total gastrin for prediction of gastric cancer. These results are presented in Figure 10, which in contrast to the teachings of the text, shows a high index for atrophic gastritis.

Table 5 presents a more detailed analysis of gastric cancer patients. Plebani concludes that there is no statistical difference between the index in early and advanced cancer, which means that there is no statistical difference between the site of the cancer in the stomach, namely antrum or fundus (see Table 5, page 307). Thus, the site of the cancer cannot be distinguished by using the markers and index suggested by Plebani.

The Examiner contends that Mulholland et al. teach an immunoassay for determining serum gastrin-17 levels in *H. pylori* infected patients in a method of screening of screening for atrophy of the stomach (ulcer). The Examiner contends that it would have been obvious to a skilled artisan to modify the method of Plebani by incorporating gastrin-17 measurements as taught by Mulholland since Mulholland teaches that serum levels of gastrin-17 are associated with *H. pylori* infection and Plebani teaches that *H. pylori* infection correlates with increased risk of gastric cancer. Applicants respectfully traverse.

Even if one were to substitute the gastrin-17 measurement from Mulholland into the method of Plebani, it would not allow determining the site of atrophy or cancer. That is, the combined teaching does not allow any conclusions to be made as to the site of the disease. In addition, the direct combined teaching of Plebani and Mulholland is that increased (due to *H. pylori*) blood levels of gastrin-17 are an increased risk of gastric cancer. This points away from the invention.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner has rejected claims 8, 17 and 26 as being unpatentable over Plebani in view of Mulholland as applied above and further in view of Deprez et al. (1992). The Examiner's discussion of Plebani in view of Mulholland is noted above. The Examiner

contends that Deprez et al. teach the use of monoclonal antibodies specific to human gastin-17 in an analogous art for the purpose of developing an immunoassay to detect gastrin-17 in tissue and blood samples. Applicants respectfully traverse.

Applicants refer to the discussion of the Plebani and Mulholland references with respect to the instant invention as presented above. Applicants further note that the addition of a specific method of measuring gastrin-17 will not fill the void left by the combination of the Plebani and Mulholland references with respect to the instant invention. Consequently, Applicants respectfully request reconsideration and removal of the rejection.

In view of the above remarks, all of the claims remaining in the case, including the newly added claims, are submitted as defining non-obvious, patentable subject matter.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), the Applicant respectfully petitions for a three (3) months extension of time for filing a response in connection with the present application and the required fee of $920.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at 714-708-8555 in Costa Mesa, CA to conduct an interview in an effort to expedite prosecution in connection with the present application.

Attached hereto is a marked-up version of the changes made to the application by this Amendment.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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LRS/SWG/sbp
0933-0166P

Attachments: Version with Markings to Show Changes Made

Exhibit 1

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner of Patents and Trademarks, Washington D.C. 20231 on: 11-15-02
(Date of deposit)

BIRCH, STEWART, KOLASCH & BIRCH, LLP

_____
(Signature)

11-15-02
(Date of Signature)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims have been amended as follows:

1. (Amended) A method for screening for atrophy of the corpus [or antrum area] of the stomach from blood serum, such atrophy correlating with increased risk of gastric cancer, [wherein] said method compris[es]ing:

a) obtaining a serum sample from a patient;

b) [determining] quantitatively measuring the pepsinogen-I [and gastrin-17 concentrations] from [a] said serum sample using an immunoassay and comparing the value[s] obtained to a cut-off value [and reference value] for pepsinogen-I [and gastrin-17, whereby a pepsinogen-I concentration in the serum sample below the cut-off value] selected from a range of approximately 20-30 µg/l, which overlaps the lower end of the reference range of approximately 25-120 µg/l; and

c) quantitatively measuring the gastrin-17 concentration from said serum sample by immunoassay and comparing the values obtained to a reference range of approximately 2-25 pmol/l for gastrin-17,

whereby a pepsinogen-I concentration [in combination with a gastrin-17 above the upper reference limit of 2-25 pmol/l is taken to be indicative of atrophy of the corpus area of the stomach, and a pepsinogen I concentration above said cut-off value in combination with a gastrin-17 concentration] in [the] said serum sample below the cut-off value in combination with a gastrin-17 above the upper reference limit is [selected from a range of approximately 0.1-2 pmol/l is taken to be] indicative of atrophy of the [antrum] corpus area of the stomach.

2. (Amended) A method for screening for atrophy of the mucosa of the whole stomach from blood serum, such atrophy correlating with increased risk of gastric cancer, which comprises:

a) obtaining a serum sample from a patient,

b) [determining] quantitatively measuring the pepsinogen-I [and gastrin-17] [concentrations] from [a] said serum sample using an immunoassay and comparing the value[s] obtained to a cut-off value [of] for pepsinogen-I selected from a range of approximately 20-30 µg/l, which overlaps the lower end of the reference range of approximately 25-120 µg/l; and

c) quantitatively measuring the gastrin-17 concentration from said serum sample and comparing the value obtained to [for pepsinogen I and] a reference [value] range of 2-25 pmol/l for gastrin-17,

whereby a pepsinogen-I concentration in [the] said serum sample below the [cut-off value for] pepsinogen-1 cut-off value and a gastrin-17 concentration in [the] said serum sample [at the lower limit of] within the reference [value] range for gastrin-17 is [taken to be] indicative of atrophy of the mucosa of the whole stomach.

3. (Amended) The method according to claim 1, [or] 2[,] or 28, [wherein the] further comprising a protein stimulation test that measures serum gastrin-17 concentration [is also measured using the protein stimulation test by measuring the said concentration at the base line situation] after fasting and then after a protein rich standard meal.

4. (Amended) The method according to claim 1, [or] 2[,] or 28, wherein said immunoassay is conducted with chromogenic, fluorescent or luminescent substrate and [the methods for

detection of pepsinogen-1 and gastrin-17 are selected from the group consisting of] absorbance, fluorescence or [and] luminescence is measured [assay methods].

5. (Amended) The method according to claim 1, [or] 2 or 28, wherein said immunoassay [the determination of the pepsinogen I concentration] is performed using polyclonal or monoclonal antibodies which specifically bind to pepsinogen-I.

6. (Amended) The method according to claim 1, [or]2 or 28, wherein said immunoassay [the determination of the gastrin-17 concentration] is performed using polyclonal or monoclonal antibodies which specifically bind to gastrin-17.

7. (Amended) The method according to claim 6, wherein a polyclonal antibody to gastrin-17 is obtained by immunizing an animal with the gastrin fragment 1-13, {Leu^{15}}-gastrin-17 or using a gastrin-17 antigen isolated from the stomach of an animal [such as a pig] .

9. (Amended) The method according to claim 1, [or] 2 or 28, further comprising an immunoassay to detect the presence of [wherein the method is performed in combination with a] *Helicobacter pylori* [antibody determination].

10. (Amended) A method for screening for atrophy of the corpus [or antrum] area of the stomach from blood, serum or plasma, such atrophy correlating with increased risk of gastric cancer, [wherein] said method compris[es]ing:

a) determining [quantitatively] the reference range of pepsinogen-I and gastrin-17 for a population of normal individuals,

b) obtaining a blood, serum, or plasma sample from a patient,

c) quantitatively measuring the pepsinogen-I concentration using an immunoassay and comparing the value obtained to a cut-off value for pepsinogen-I selected from a range that overlaps the lower end of the reference range; and

d) quantitatively measuring the gastrin-17 concentration from said sample by immunoassay and comparing it to the reference range for gastrin-17,

[concentrations from a serum sample and comparing the values obtained to a cut-off value and reference value for pepsinogen I and gastrin-17,]

whereby [a] if the pepsinogen-I concentration in [the] said [serum] sample [below the cut-off in combination with a gastrin-17 above the upper reference limit is taken to be indicative of atrophy of the corpus area of the stomach, and a pepsinogen I concentration above] is decreased compared to said pepsinogen-I cut-off value [in combination with a] and the gastrin-17 concentration in [the] said [serum] sample [below the cut-off value is taken to be indicative of] is increased compared to the gastrin-17 reference range, then atrophy of the corpus [antrum] area of the stomach is indicated.

11. (Amended) A method for screening for atrophy of [of the mucosa] the whole stomach from blood, serum or plasma, such atrophy correlating with increased risk of gastric cancer, said method [which] compris[es]ing:

a) determining [quantitatively] the reference range of pepsinogen-I and gastrin-17 [concentrations] for a population of normal individuals,

b) obtaining a blood, serum or plasma sample from a patient,

c) quantitatively measuring the pepsinogen-I concentration using an immunoassay and comparing the value obtained to a cut-off value for pepsinogen-I selected from a range that overlaps the lower end of the reference range; and

d) quantitatively measuring the gastrin-17 concentration from said sample by immunoassay and comparing it to the reference range for gastrin-17,

[serum sample and comparing the values obtained to a cut-off value for pepsinogen I and a reference value for gastrin-17,]

whereby [a] if the pepsinogen-I concentration in [the] said [serum] sample [below the] is increased compared to said pepsinogen-I cut-off value and [a] the gastrin-17 concentration in [the] said [serum] sample [at] is within the gastrin-17 reference [value for gastrin-17 is taken to be indicative of] range, then atrophy of the [mucosa of the] whole stomach is indicated.

12. (Amended) The method according to claim 10, [or] 11 or 31, [wherein the] further comprising measuring serum gastrin-17 concentration [is also measured] using a [the] protein stimulation test that [by] measures[ing the] said concentration at the base line situation and after a protein rich standard meal.

13. (Amended) The method according to claim 10, [or] 11 or 31, wherein the methods for detection of pepsinogen-1 and gastrin-17 concentrations are determined by are [selected from the group consisting of] absorbance, fluorescence [and] or luminescence [assay methods].

18. (Amended) The method according to claim 10, [or] 11 or 31, further comprising determining the presence of [wherein the method is performed in combination with a] *Helicobacter pylori* [antibody determination].

20. (Amended) A method for screening for atrophy of the mucosa of the whole stomach from blood serum, such atrophy correlating with increased risk of gastric cancer, which comprises:

a) obtaining a serum sample from a patient

b) [determining] quantitatively measuring the pepsinogen-I and gastrin-17 concentrations from [a] said serum sample by immunoassay; [and]

c) comparing the pepsinogen-I value[s] obtained to a cut-off value selected from the range of approximately 20-30 µg/l [for pepsinogen I and a reference value of 2-25 pmol/l for gastrin-17]; and

d) comparing the gastrin-17 value to a reference range of approximately of 2-25 pmol/l for gastrin-17,

whereby a pepsinogen-I concentration in [the] said serum sample below the cut-off value and a gastrin-17 concentration in the serum sample at the lower limit of the reference range [values for gastrin-17 is taken to be] is indicative of atrophy of the mucosa of the whole stomach.

21. (Amended) The method according to claim 20, [wherein the serum gastrin-17 is also measured using the] further comprising a protein stimulation test [by] that measures[ing the said] serum gastrin-17 concentrations after fasting [at the base line situation] and then after a protein rich standard meal.

22. (Amended) The method according to claim 20, wherein said immunoassay is conducted with chromogenic, fluorescent or luminescent substrate and [the methods for detection of pepsinogen-1 and gastrin-17 are selected from the group consisting of] absorbance, fluorescence or [and] luminescence is measured [assay methods].

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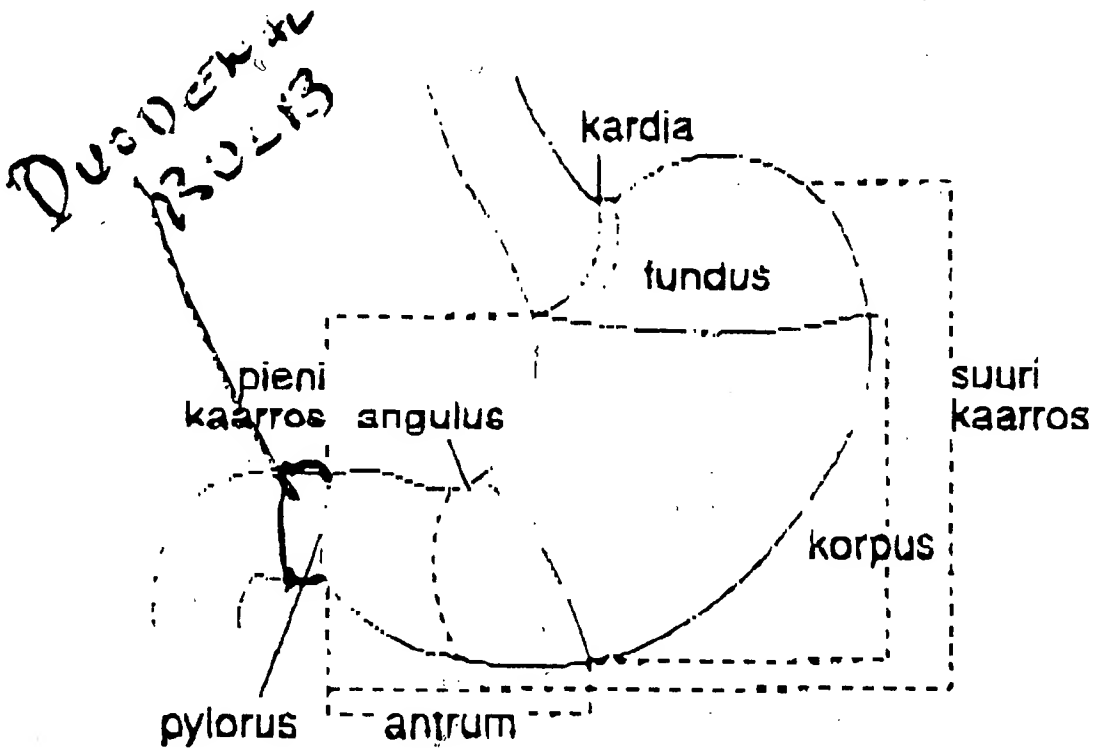
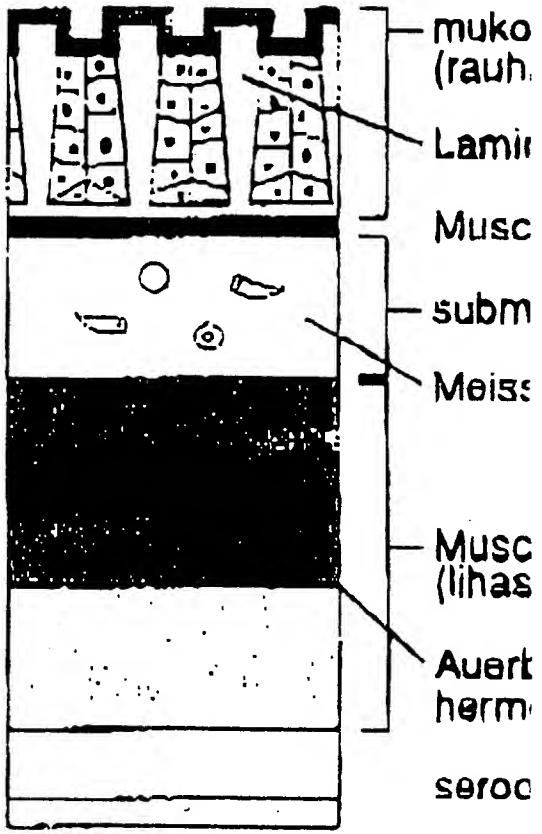
kenteesta antrum- ja korpusalueilla on esitetty kuvassa 3. Sekä antrumissa että korpuksessa mahan limakalvon pintaepiteelin mikroskooppinen rakenne on samanlainen: epiteeli muodostuu PAS-positiivisista.

Exhibit 1



Kuva 1 ■ Mahalaukun eri osat.

Mahalaukun kor... solu on toiminnallisesti



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